Brown, Paul 2004

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Dr. Paul Brown Interview

Office of NIH History Oral History Program

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Interviewee: Dr. Paul Brown NINDS

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Maya Ponte: Prior to joining the lab here, where did you go to school and what were you doing?

Paul Brown: Well, I went to Hopkins. And the anatomy professor, Dr. David Bodian was a very serious guy but he was a very, very, very good scientist. He probably should have shared the Nobel prize for the polio discovery. He had been in the school of public health, he actually became a professor in anatomy. He is most widely known for inventing a method to stain for axons using a silver-protein complex called protargol. He was a very bright guy. But he got involved in the whole polio issue and he was using monkeys -- chimps, and it was he who discovered that the reason all of the vaccines were failures was because there were three different strains of polio. A vaccine, in order to be effective, it had to have a combination of antibodies. I mean, that was a fabulous achievement.

MP: Sure, yeah.

PB: That's just background to say that he was very serious researcher. I started as a freshman the summer between my freshman and sophomore year I was penny poor. I was destitute. I was on a scholarship and I needed money and there were summer research positions. I thought that would be a very interesting way to use my summer, and I'd also become interested in what was still called blood/brain barrier. It struck me that this was a very interesting phenomenon and so I did that. I got to know him because he was a very unapproachable guy. It was funny because he was probably a very generous and warm person but there was something about him that made you refrain a little bit until you got to know him. I continued doing research, and then I was, second or third year, I went back to the department -- oh, and I got to know -- I liked the people in the department. I went back with another student and I undertook two special sections. And again, this got us more and more friendly. And then I was accepted as an intern at the hospital.

MP: In what year was this?

PB: 1961, and then was accepted as a resident, so that was '62. In 1962 the military began drafting residents' right out of the hospital. We didn't have any particular sense that had we been kicked out of residency we would be shipped off to Vietnam, although we're designated sometimes. It really had nothing to do with being afraid of Vietnam because we weren't thinking about Vietnam. Vietnam was small potatoes at that point. What we didn't want to do was to be -- with all of our training -- in a position where we were in some base in Louisiana treating. And that's what a lot of people were doing. It just struck us as a horrendous potential waste of time, to be drafted and just sort of clocking in the time. So many of us looked for alternatives to that, and I went back to [inaudible] and told him I was not interested in doing basic research but something else, and that would satisfy the military. We really were looking for ways to circumvent the draft. So I asked if anybody in research at the National Institutes of Health or public health service. Public health services served the purposes of the draft.

MP: So anyone working at the NIH?

PB: Any public health service officer. Public health service is only a very small fraction of the professionals. Most of the people at the NIH are civil servants. But at that time the public health service was much bigger than it is now in terms of the network of public health service hospitals. It included the Indian Service, prison service and CDC. This is what the Public Health Service was all about and having done research, knowing that I enjoyed research, what better way to satisfy the military requirement. In this course of the conversation, someone said, "Well, there's a guy down at the NIH." and he'd done an interesting study called [inaudible]. So I wrote a letter and didn't hear back. And then -- because he was in New Guinea, and I wrote the letter -- I wrote the letter, and they forwarded it. I got a phone call and he said, "Why don't you come down" and I went down to building [inaudible] and there were offices, basically it was just a hallway, [inaudible] and he sat in one chair and I sat in the other and we just started talking. I stayed, I don't know, three hours, four hours. I didn't say anything. He [D. Carleton Gajdusek] is a fascinating guy, no question. I was enthralled by the way he did a number on me. It wasn't any great, phenomenal intrigue and mystery in who he was. It wasn't the subject that was as much as the passion and wide-ranging interests that was so exciting. All kinds of things and in fact, the first thing that I studied, the very first project that I was put on was to get knowledgeable in terms about the testing for measles. He had just come back from Papua New Guinea in the Pacific Islands. There was a question as to whether measles vaccines would be durable in the absence of natural circulating antibodies. I learned the month that I first went there -- this was now 1963, and 1963 happens to have been the year that of the first chimpanzee inoculations. So I knew about it but that wasn't what really interested me. What really interested me was conduction of viruses. So I studied the measles and he sent me off to the Pacific to immunize isolated populations. And I did that, I came back, I went over -- I learned how to do the testing over July and August, and then I went over there and spent the month of September, having never been out of the country before, that was an experience. And I came back, it was a successful trip, everybody was happy, and the next thing I did, I was home for about a month, they sent me off to New Guinea to collect samples, or as many as I could of these tissues. So again in November I was in New Guinea. I was in New Guinea on the trail. At that time, we had no idea [inaudible] but that's the reason I was there, because since we hadn't had or he hadn't had any transmission.

MP: And had he always?

PB: Well, mostly including a monkey or two. But these weren't held long enough. One idea was, "Well, we're not [inaudible]." So we had to go to an absolute optimal so we had a whole line, a kind of supply line of liquid nitrogen all the way from the hut where this woman was dying. I mean it ran through the hut, which means the small little town, to Port Moresby in New Guinea, down to Sydney and Melbourne in Australia, and then down. So we got the brain, it was in liquid nitrogen within an hour of death and it never got out of liquid nitrogen. Now we know I could have put it in my pocket and brought it back rotten and it still would have been viable. That was one of the first.

MP: So he sent you there to collect one of the critical samples, one of the very first ones that they were going to inoculate and leave the animal live for long enough, so had he been communicating with you at this point?

PB: Oh, sure. The connection was there. It evidently took two or three years in order to get chimpanzees, go get them. It took time to establish a facility. In fact, those chimpanzees were kept which at a wildlife reserve. But they had to be prepared. It wasn't an overnight thing, and so it obviously took about three or four years to do that, and as it happened, [inaudible]. I think before I came back they [inaudible].

And then after that I did some work on pathogenesis and it wasn't really until -- well, and then I got involved in doing a lot of antibody testing of serum, both from the patients with naturally-occurring CJD, looking at every conceivable virus. Then we did the examination of measles antibody in patients with multiple sclerosis. It wasn't really until I went to France for the first time, in 1971, that I really totally focused on.

MP: What happened then?

PB: Well, as I just said, in the years before that I'd been doing a lot of testing, laboratory testing. And I think it may have been Carleton's suggestion that there have never really been good systematic steps of [inaudible]. He would go around talking about [inaudible] on the basis of very, very fragmentary information. And I think he just thought that I might like to do it and I don't remember what there was that I had done that [inaudible] I don't even remember. [inaudible]. Yeah -- well not quite, four or five years. [inaudible] But I guess I must have [inaudible] I remember I gave a lecture on [inaudible]. So I liked it. I liked a lot of things [inaudible], he knew [inaudible] you know at that time [inaudible], maybe she [inaudible]. Oh yeah. I'll get into that in just a minute if you want to turn your phone off.

To recapitulate, in the early years I did a lot of other things besides virology. When I came back from France, there was kind of a period where -- after the demonstration in the 60's there were a tremendous amount of experiments that were going on that examined the pathogenesis of slow viruses and so forth, and I was doing stuff that, in retrospect, it was okay but it was far from [inaudible] trying to figure out if we could purify something that would still be infectious. We were using [inaudible] and we just never really got much headway in purification. Hundreds of animals were being inoculated all the time, but it was, after the first few years along, around -- just about the time that got Carleton the Nobel prize in 1976.

We were all sort of running out of things to do. All of these pathogenesis experiments had been done. We were looking at [inaudible] we were looking at how many tissues were infectious and, you know were [inaudible] but after three or four years, there wasn't a whole lot more to be done in that sphere and none of us had any really good ideas about where to go. So I decided to go back to France and now I have to revise what I've said before because I made a mistake. I made two trips to France. It was the second trip that was '77-'78. There had still not been any good [inaudible] but we had a much better idea now, we could do the [inaudible]. [inaudible] made for the express purpose of examining the relationship, if any, of interferons and interferon antagonists in the brains of infected patients. So this was still -- the first trip I made, the first one was strictly laboratory bench work. We were still looking for associated phenomenon that we could perhaps distinguish abnormal brain tissue. So the first trip I made to France really turned out to be, in a sense, a waste of time. None of it worked out and looking at other things I kept looking at interferons.

MP: So this is -- wait, this is when you came back from the other trip?

PB: First trip.

MP: First trip, okay.

PB: And those were active times. I can't remember what I was working on but after he got the Nobel, which was in '76, then there was this kind of hollow period, and I actually was casting around for things to do. And I hit upon, well why don't I do a generalized review of hepatitis which took me a whole year to do, published in a totally obscure journal. And it took an enormous amount of work to do it. I don't know if anybody ever read it or found it useful, I looked at it the other day and thought it was rather good very exhaustive compilation of everything that I knew and was known about various varieties of hepatitis viruses. It was, you know -- it was a great reference work. But it was done because I didn't know what else to do.

MP: Did you want to do something where you were working on the review?

PB: Yeah, well, I didn't know -- that was strictly a library thing. Of course I had knowledge. I knew a lot just having been to most of these places, you know, but the Philippines yes, all of these places were familiar to me. I don't know what there was about hepatitis, actually but I mentioned it because I know that it represented a kind of default initiative. I had no further ideas as to what to do in the field of virology.

MP: I'm just really curious about that. You said that the lab had already done a number of studies on pathogenesis, they'd done a number of studies on transmission.

PB: The laboratory was very much flavored by Carleton -- I guess I would say biased towards biology rather than molecular biology, and I think to this day his research during a period at a time when molecular biology was growing recognized that what was going to be needed. He set up shop to do that. He could have, if he had chosen to, gone in that direction but he chose not to. I went in the same direction, that is, I didn't have the training, expertise or even the desire to get into the molecular biology. I just didn't have the tools, I didn't learn it. And so I went in a direction that was in the opposite direction of molecular biology, which was epidemiology. You've got these levels. You've got molecular biology, you've got biology and you've got epidemiology. There's not much. Also, bear in mind that through the whole thing, that I was formally trained as an intern; and that certainly played a part in the pleasure and the skills that I brought to the French experience in '77 and '78. I had gotten involved in a lot of virology. Carleton wrote a couple of pretty damn good clinical articles on CJD back in the late '70s. So it's really clinical and epidemiological at that level.

MP: I would like to talk more about that, about when you started working with the patients seeing clinical patients.

PB: Well, the first clinical patient I saw was deceased.

MP: When you went and collected that brain? What did you see? I'm sure it was an incredible experience altogether.

PB: What I thought was that this was that's what it was. Devastating but not fascinating, it didn't fascinate me. I saw this as another disease that could devastate a population, but there wasn't any particular human prevention because I couldn't communicate.

MP: I see. So then when did you see your first case of classical CJD?

PB: I would say about my visit in France.

MP: Do you recall your impression of maybe not that patient, but one of your first several cases that you saw, did you notice anything interesting, like did the variability strike you, or what kind of feelings did you have?

PB: I'd have to say that it wasn't anything remarkable. I was an internist. I'd seen hundreds, and maybe a thousand different diseases, and many of them were serious diseases and the reaction of people and families with serious diseases is always predictable and it has to be dealt with.

MP: The reason I'm asking is because people with family members who have CJD say, "Oh this is the worst, and I've never seen", and I just wondered, in the context of your experience how you saw it.

PB: It was bad. It was a bad disease.

MP: But it wasn't like it was different from someone with another terrible disease.

PB: Exactly.

MP: Okay.

PB: And my interest was with protein. As an intern, having to go out, there was a little room at the entrance to one of the wards, and and there was a sofa here and the door was here and the chair's over there, very grim. This room was filled with the black relatives of this young black 25-year-old man, probably about 10 people. The patient died and this room full of people were there and I went out, it was my responsibility to tell them, and none of them were anticipating this. I mean, there's just no way that you can break the news that their loved one is dead except by saying, "I'm very sorry." Well, I'll never… the reaction -- it was as though I was in a war. I was almost assaulted, people were flopping on the floor, they were screaming, they were yelling -- not necessarily angry but they were just in hysterical shock, and there was this little black boy in the middle of a family reunion of the most enormous grief that I'd ever seen in my life. After that, nothing that I ever saw in any situation of CJD was comparable. I was cured by fire -- that was an experience that I'll never forget and nothing's ever been worse than that. The families -- I sympathize with it, and I think I can -- far better than almost anyone I know in this country deal with and sympathize with and give information in a correct way to explain.

MP: Can you tell me a little bit more about your second trip to France, when you did your first epidemiology?

PB: That was a blast, that was a blast.

MP: What was that like? What kind of stuff, the day to day, were you doing?

PB: Well the day to day was we went into the office in the hospital, we had a nice little suite of rooms, and a couple of cabinets to construct a retrospective study of all of the cases that we could lay our hands on. And it took us a month, or two or three, to refine our approach to this. One of these approaches, we went to a statistician. He was going to set up a whole computer program to. We were just going to have to do it -- get our hands wet and our feet dirty and just do it. So we set up maps on our walls and had a supply of pushpins. I guess we called every single neurologist in France, and we started writing letters, but mostly phone calls, which was shocking to the French because they don't do business this way. They sit at a desk and send letters -- not make phone calls. Using Francoise's extensive friendship and knowledge of the community, we made three separate, sequential tours of France -- that was after the phone calls. We wheedled them into accepting us so we visited every neurologist in France, more than once in the course of this work -- always coming back, always looking, always going to the records. But it paid off because I think we probably produced the best study to date, and it will probably remain the best study. So when the Europeans started they didn't get numbers that were any different than what we got. They still haven't, actually, but they've now increased in numbers, and they've pushed the incidence -- the true incidence up. For us, that was an absolute maximum. So we're in the same range, and in fact it's the same range that Carleton was blabbing about without adequate data to support it.

MP: Really?

PB: Yeah.

MP: Where was he pulling the data?

PB: There was an anecdote, a little thing that Helena had done in Italy and probably something that Bob had done and I think Carleton had, in his travels, talked to neurologists who said, “Well, we had many cases.”. It’s also the number that had come up. I mean, 1 in a million is the incidence of it and it has been described as a 1 in a million about 1975.

MP: What do you think of the issue of reportability, and whether the data was reportable, whether that would stay and whether that would actually change?

PB: Well it would certainly make it easier. It would corroborate the diagnoses.. I don’t think it would change anything very much, for three or four years now and at the moment he only had, he estimated, about one third of all the cases. Jesus! That’s pretty damn good! To get one third of all the tissues from one third of all cases of is phenomenal. I don’t think it would change very much, for all the reasons that I’ve just mentioned. I don’t think overall we would learn any more from the other two thirds. If you’ve got a third of the cases, you’ve got 100 cases. What are you going to do with another 200 cases? You can’t even use the 100 that you’ve got. So here Luigi is making the case for a complete collection and I don’t think he knows what he would do with them if he got it. I’ve never heard him say what he would do differently with 100 cases. Maybe I’ll ask him in public, because he continues to say this and he continues to encourage people in the CJD Foundation and that proves that there’s this massive underreporting and that if only people would give him 100%, if only it would be a mandatory reporting then we’d get the true figure. Jesus Christ, we know what the true figure is from Europe! The US isn’t going to be any different.

But I like Luigi, he’s a nice guy and I really don’t want to offend anyone in public. As far as I’m concerned, if he gets 100%, so much the better for him but I don’t think it’s going to help him. It may reduce the stakes, it may. It may reduce the number of angry relatives who say they’ve had that experience. Maybe it would reduce that, but just making it mandatory to report will not do the job. There are diseases that are mandatory reportable diseases that as interns, we never reported. That’s true of all reportable disease, with a couple of exceptions. But reportable for years. Practicing clinicians do not like the extra burden of having to report a disease, and that’s just a fact of life and they’re going to have to deal with it.

MP: When you were doing this study in France, were you collecting tissues?

PB: When they were available. Any case of CJD that was occurring during that year we tried to get the tissue.

MP: Oh okay, so did you have to talk to the families to get the tissue or did you go through the neurologists?

PB: Let me think. In France, I believe at that time and maybe still, patients are so intimidated by physicians that it was more like, “We’re doing an autopsy,” not, “Can we do an autopsy?”

MP: Okay.

PB: That’s my recollection and I think that’s probably accurate.

MP: What about in the US? How did that compare to your experience? I mean, did you have to talk to the families?

PB: Oh yeah, sure. Well I didn’t -- or sometimes I did when the patient was still alive, but it wasn’t I who actually asked for the autopsy, it was in the hospital. So yeah, I think probably that went on and if I thought it was important I would tell them I thought it was important.

MP: Was it harder in those days to get pathologists to do an autopsy on these cadavers?

PB: Sometimes.

MP: Really?

PB: Oh yeah. Asking for an autopsy, Dr. X, Dr. Y and Dr. Z all run away with their hands in the air. Yeah, that was terrible.

MP: So that's been an ongoing problem ever since disease has been found?

PB: Well my attitude about that is that it comes with the turf. You don't have to take unacceptable risks, but that isn't an unacceptable risk and if you're not willing to put yourself on the line to accommodate a family and possibly benefit future generations -- we don't know. What we do know is that basically an autopsy -- the confirmation is a very important thing. I can still remember Hanneman [spelled phonetically] had a problem. I remember really getting furious that he was defending the fact that it was a very risky thing. I remember, I didn't get angry and I actually told him if something which was entirely controllable and manageable then they shouldn't refuse. I really didn't like that.

MP: As you started to get more involved in the field, when did you start attending conferences?

PB: Well the first conference I ever attended the competing British attendees almost physically assaulted each other. That was the first one.

MP: What was the main controversy over?

PB: Genetics.

MP: And that was Perry?

PB: Perry versus Dickinson versus Stanford. I don't know who else.

MP: Okay. And it was basically genetic versus?

PB: It was genetic versus horizontal gene transfer.

MP: And then after that do you recall any others?

PB: By and large, everything that I was doing in the early days in the laboratory would be presented somewhere or other, whether it was the American Society of Epidemiology or another. There was -- in fact, you probably have never seen that -- a monograph. The second NIMS, a green book. It was a monograph and it was a meeting that Carleton organized. And it was on slow viruses -- slow and unconventional viruses, it was held here at the NIH. It's the only meeting that I know of that the NIH has ever held on the subject, and I think it was 1964. The NINDS Monograph *Slow, Latent and Temperant Viruse Infections*. NINDB Monograph No. 2., 1965.That was before we knew it could be transmitted. A good monograph. I can't remember when I got to a point, certainly after 1985. I did and a fair amount of work on that research.

MP: When did you start?

PB: Well that was when Rohr was here.

MP: Okay, so he came from CalTech?

PB: Yeah, I'm not sure why. I guess because he knew how notorious it was and we wanted to do a more systematic study using some of the old standby methods as well as new. Yeah, we looked at new and then subsequently looked at one of the few original ideas. Not really original but I did have this inspiration one day that inasmuch as formic acid enhanced the staining of protein, formic acid was pretty tough stuff and maybe could also inactivate the experiment and as far as I know it's still used in the world of neuro.

MP: Really? That's fantastic.

PB: Fixing tissues, when you're working with tissues that are tough suspects or definitely known to be [inaudible].

MP: And so you started publishing that in the '80s?

PB: I only published one paper.

MP: Published one paper and it just spread?

PB: Yeah, well the neuropathologists required evidence.

MP: Well that's amazing. What about in terms of inoculation? Were there any innovations made during the process -- you're talking about how with the mouse doing intravenous inoculation you have to find a vein in the tail, but just in terms of either intracerebral or I; do you remember in the process of doing these experiments any ideas or methods that made it easier to do the inoculations?

PB: No, and no one figured that out -- there aren't any. There are just so many ways you can put a needle into an animal. There was no novelty whatsoever; peritoneal, subcutaneous, and cerebral are all well-known routes.

MP: Can you describe to me the peritoneal, how that works?

PB: Sure, you just pop it in the belly and push.

MP: Syringe?

PB: Sure, just like intrarenal. You lift up so you're not inoculating directly into the intestine or the liver or whatever -- there's a lot of room inside.

MP: You just take a syringe and just inject?

PB: Yeah, you know, sort of go into the backbone -- you go in the side and you go in gently and you move it a little bit to be sure that you're not in an organ that you don't want to be and then you can put in. It disappears very quickly in the intestine.

MP: So presumably you're injecting it into the lumen of the intestine or is it in the wall?

PB: No in the peritoneum.

MP: It is in the peritoneum, directly in the peritoneum?

PB: Sure. It's intra-peritoneal.

MP: How do you know you're in the peritoneum? Can you just feel it?

PB: No, but it's what you don't feel -- your needle is not fixed.

MP: Okay.

PB: Now, I suppose you can make a mistake and probably pop it into the intestine. But typically you go in and remove just a little bit, just to know that the needle was free and then you pull back a little bit and be absolutely sure so that in fact it is the peritoneal cavity and all the stuff is in here. You're right there at the edge of the peritoneal cavity. There's no trick to it.

MP: Does that give pretty standardized incubation times?

PB: Yeah.

MP: So the figure you quoted and often people quote with the IV would be about a 10^{th} as efficient as the IC would?

PB: That was our experience, but…it may, in fact, still be the only quantified experiment which has been published except one work comparing IV and IC and intraperitoneal and others. One of these experiments was widely quoted. There was something about an IV / IC comparison, and I haven't looked at the papers for a long time but it said that really they weren't absolutely comparable. But let's suppose they were. It was found that the IV, as I recall, was less efficient and possibly 10 fold -- I think it was 10 fold less efficient, and so we may have been the second but we were of course using blood and not brain, which is more indirect. And so we found that we needed 10 times more infectivity to get a transmission from IV than IC. You have to be very -- well, you have to be careful to not to make flatfooted statements based on incubation rate. This is what people tend to do where they haven't quantified anything. In the sheep for example -- yeah, in the sheep they were getting incubation periods that were about the same range whether they inoculated brain or blood, okay? And the assumption was therefore that there might be a high titer of blood, but until you've titered it you don't know. Other studies inoculated brain IC and IV and gotten, as I showed on one of the slides, incubation periods that weren't too different. They interpreted that to mean that the intravenous route was a fairly efficient route and I have no quarrel with that, but it still doesn't tell you how efficient and until you've actually done this sort of experiment.

MP: You mean an actual titer experiment?

PB: Yeah.

PB: We didn't have to do a titer because everything we did was undiluted because there was so little infectivity. We didn't need to titer it out, all we had to do was compare the number of takes -- you know, in brain versus in blood. You inoculated 100 mice and got three takes from the blood and 30 takes from the one with IC -- well that's the answer.

MP: You have the number it was already an endpoint. When did you first start doing experiments with blood?

PB: That's probably the other smart idea I've had and I don't know why. I don't know why to this day exactly what prompted me to get into blood before blood had become a trendy topic, but I was ahead of the game with blood. And it may have been just as I became aware that nobody had really looked at blood and particularly the incubation period of blood. Then Dr. Kuroda, a Japanese researcher, had to come to our lab and he was interested in finding what parts of the spleen were most infectious. So the focus of his paper was to separate spleen components and measure infectivity, but in the course of that he did have 4 or 5 points during the incubation period phase of disease for buffy coat and there was some infectivity in this model about halfway through the incubation period. So we had that information but that was it. There was that one experiment that was looking at incubation period and until then as I recall -- I'm trying to think if anyone had found infectivity in the blood before Kuroda. It's possible that nobody had.

MP: That's amazing.

PB: There may have been one isolated report as part of a huge report back in the days when they were doing scrapie in sheep but -- and I think it's possible that [unintelligible] had already begun looking at blood and getting funny results. I think it just occurred to me that this issue needed a good thorough airing and we had in our laboratory a mouse model that would allow me to do that.

MP: And which was the mouse model?

PB: Well that was the [unintelligible] strain. It was the same model that Kuroda has used. It was the GSS strain [Gerstmann-Straussler-Scheinker] disease adapted to mice in Japan that Kuroda brought over and it's been used widely in Japan and sometimes by other people. This was the discussion that was pointing out that this might be an unusual strain and what he was implying was that this rule couldn't be taken as representative of a sporadic issue, I found nothing wrong with that. In fact in retrospect the whole discussion was totally unnecessary because I made the mistake of saying that our patient was a GSS patient and it but it wasn't the Japanese patient that looked differently. But it's still GSS, it's not sporadic occurrences.

MP: Got it.

PB: We did have two sporadic CJDs and they still haven't transmitted, but the transmitted case was in fact a mutation front CJD to GSS and it is a funny thing, but it's not the one we were talking about.

MP: So, can I just ask you just as a point of clarity -- so has CJD ever been transmitted to rodents that you know of?

PB: Nope, not that I know of.

MP: It just hasn't been tried I'm sure.

PB: I'm not even sure we tried. I really have to look. If it had I probably would have mentioned is as a reference in one of the few papers that we wrote

PB: I have given to anyone who would listen a substantial amount of verification of what I have been saying until this year, but I think in 2003 I brought these three observations that are brand new -- four, actually -- and they involve the newly discovered fact that blood is infectious if there's enough of it. And you must evaluate ERP before infectivity, before a study is particularly interesting because you wonder whether or not it is in the blood. They showed that it in fact it was in muscle fibers. It's in the muscle, at least in the experimental model. So what I think has happened is two things. First, in terms of blood, is that if you give a large volume IV, even if it's not as efficient at removing infection as an IV, you wind up nonetheless with somewhere between 10 and 100 times as much infectivity going into your specimen, which is going into a bioassay animal, that is just plain arithmetic.

MP: Is that's just because the animals that you worked with were smaller?

PB: You can't put more than about a 10^{th} of an ml into any animal including humans and chimps. They're big animals and they don't do well. Comparatively speaking, you can put a gallon into a rodent and, as you can weight for weight with a chimp. Apparently the higher animals just don't react well. Maybe you can give more to an infant, which is what we're doing with erythromycin and I think they're still probably expanding it a bit. Whereas the adults are not and as for primates, we are always inoculating animals that may be young..

MP: So we're talking about IC inoculation?

PB: IC inoculations. The phenomenon is sudden death if you give too much. In chimpanzees if you give more than a 10^{th} ml you are taking a risk considering that you can give mice 500 ml -- let's just say 100 ml with the same animals, if IC is $1/10^{th}$ less effective then you're still ahead of the game from a 10^{th} to 100. You know, that's 1000 fold factored by $1/10^{th}$ the effectiveness. This wasn't widely appreciated. Nobody thought much about it. I didn't and nobody else did either. We did get the maximum amount into an animal which tended to be some IC and some IV, but the IV was never a transfusion model.

MP: How much could you give?

PB: IV, maybe in a mouse? We might give a 10^{th} of an ml. That's not much. It's 100 microliters. Maybe $2/10^{th}$ of an ml, if we could get it, but the problem there is not the skill and given more and the skill to do it, but putting a .27 gauge needle into the tail vein of a small mouse is just difficult. Now if you work with hamsters like Rob Grower [spelled phonetically] you've got a an easier time -- you know, a systematically developed technique where they access an artery, you know it would be the equivalent of a transfusion. Even then, he doesn't get many transfusions -- 100 or something like that.

MP: Yeah, exactly.

PB: So the sheep actually turned out to be a more susceptible animal. It had more infectivity than rodents. Now we have the transgene. It's pretty clear that the people who are using the pathogenic as the basis for statements, as I have myself in the past, that blood is simply not infectious, muscle is simply not infectious, are going to have to do an about-face, as I've done. So it's painful to do an about-face, but what the hell, if you get new information it's silly to just stand by the situation as of a year or two ago as opposed to the situation that we now know exists. So my message is now "watch out" because -- you'd better watch out for blood in any in any species and you'd better be careful about muscle and you get blindsided if you're not expecting it. So they're not happy about that, but they understand and be prepared for it you're in a much better position. They can start thinking about ways to combat it and maybe this high pressure thing that we're doing is going to be a decent way to get at that problem. It's a strategy, the only strategy less important their own. I don't think it's going to happen, but if it did that would be the only other strategy.

MP: I was just going to ask you about that. So do you still feel -- I mean in light of the new evidence with blood in the UK, how do you feel about positive products?

PB: I feel very comfortable.

MP: And can you expand on that?

PB: Blood components are crude components. Nothing is done to them except centrifugation and they're administered as such. Positive products fail in the process, which in every instance includes at least one removal step. Usually that removal step is a chromatography step. Sometimes it' s a filtration of one sort or another, sometimes it's centrifugation; and though as you go down, the cone fractionation you're already getting rid of massive amounts of infectivity in the experimental spike. Even in the infectious plasmid itself that is from infection, as you move down the cone fractionation plasmid you start out with 10 to the 20^{th} infectious units and fairly quickly you're down to nothing. If you start out with spike blood and go through cone fractionation -- spike it with 5, 6, 7 logs, by the time you're down to albumin you have nothing. So that's the vertical and at each fractionation step there's this kind of horizontal processing before you get to final product and all of those processing protocols include these extra steps.

MP: What do you mean by horizontal processing?

PB: Well, you know, I look at it -- and I've got a slide in the other room -- if you start with a plasmid and you down a cone fraction each of those steps, for example cryoprecipitation, is then processed.

MP: It goes through another set of steps.

PB: I look at that as the horizontal.

MP: Got it. I see.

PB: So you've got a ladder without one sort of down this way and then we've got a series of protocols. So I think we've got enough evidence of four or five different protools all of which say the same thing and that same thing is that at a minimum we've got something like 3 log per ml and that's well beyond anything we expected ever to occur?

MP: Because I guess -- the other thought I had is, what you think about whether or not there is a threshold dose and how that comes into play in thinking about blood components and blood products.

PB: Sure. Well I don't think you need to because I think the removal capacity of these steps will do the job even if there were quite a lot of infectivity, but there is a threshold experiment, evolution experiment. Nobody has done that experiment. I've been trying to do it indirectly for four or five years, which is to take a ml, 1ml, of a sample of the brain with some blood. Blood would be a better thing to use because we already know in mice, for example, that in the clinical stage of disease in mice the maximum amount of plasmid is about 20 doses, 20 infecting doses. So you're already starting at a nice low level. Now you take that ml or let's say you take 2ml and the 1^{st} ml you give to 30 mice, because you would take 1ml and distribute. The whole ml goes into 30 mice. Now you take another ml and you dilute it 1 to 10 and put it into 300 mice. You inoculate the entire amount, still.

MP: So this is looking like an expensive experiment.

PB: Well I've done the arithmetic and in fact with a shrewd guess and a little luck you could probably do the experiment with about four or five hundred animals, which is a big experiment but it's doable. I've done any number of experiments with about hundred animals.

MP: So you wouldn't need to go to the stuff?

PB: Well I think you would and that's why you wouldn't start with an MF.

MP: I see what you're saying.

PB: It's a doable experiment and it answers the question. If you cannot -- if it requires only one and that particle is randomly distributed it can cause an infection, then you should see the same number of infections no matter how large the dilution. If, however, it takes more than one circulating particle or if the particles are heterogeneous -- if in the circulating blood you've got a particle that has 100 molecules and another one that has 10,000 molecules, 20 others that have 50 molecules -- maybe it takes a certain number of molecules. It looks like it does. It looks like that way. You run out of detectability at the point when you still have, in the best hands, at least 1,000 infectious doses left and people have used a couple of experiments to indicate that it's probably somewhere between for a single. It's entirely possible that you can't, in fact, dilute a specimen to below the threshold.

MP: But until that experiment is done --

PB: Until it's done nobody is going to be able to say one way or the other.

MP: Exactly. We can only say that based on certain experiments.

PB: But we can't even say that. It's based on nothing. There's no basis to say one thing or another. None.

MP: It amazes me that that experiment has never been done because I've seen this issue come up.

PB: I've tried to get the New York people to do the research to do it. I ran out of NIH support..

MP: When you first heard about the UK case what did you think?

PB: I said, "Damn."

MP: Were you convinced when you first heard about it?

PB: Oh yeah.

PB: -- I only read it once and I said, "Okay that's that."

MP: You had no doubt?

PB: And the thing that persuaded me was the age of the recipient.

MP: Because it was unusual?

PB: Right, late sixties.

MP: There have been two other cases that I can think of.

PB: One in ‘72.

MP: One in ‘72.

PB: And one in about ‘53.

MP: Okay.

PB: And all the rest were younger. You know, they did the statistics and it was about 1 in 20,000 of two cases occurring and given the age two cases from aural exposure or whatever the usual exposure as opposed to an antigenic blood transfusion 1 in 1,000. So, that makes the number crunchers happy, -- quite frankly I did not pay much attention and still don’t whether it’s 1 in 1,000 or 1 in 500 or 1 in 100,000 it doesn’t really matter, it’s unusually rare. All we know blood and the incubation period, it’s just too good to be true.

MP: Has your thinking at all changed about sporadic transmission?

PB: Well, I think that has to be examined, but as I said it’s going to be very, very difficult to prove even if you go after it and people have gone after it. I mean there’s all kinds of statistical evidence and individual so-called look back efforts against the phenomenon of sporadic having blood infectivity frequently enough to be detected. Nobody can ever say that one case ever occurred statistically. You can’t detect one case on the basis for statistics it just won’t happen. So, what we need is a classic sporadic transmission giving it blood to someone who’s at least 17 years old and that person coming down with it, there’s your luck, just the reverse situation. But that’s the sort of case that will essentially prove the point of sporadic. It won’t change a whole lot because if it’s that rare that we can’t pick it up even when we’re looking for it based on the incidence of CJD being in blood recipients and the incidence of CJD being in donors. The incidence of CJD being in all these cases where donations have been made and the patient gets CJD four or five years later. Nothing -- I mean, for blood components I’ve seen a couple of numbers but I’ve used a smaller number because it’s the most conservative. There have been over 100 incidents of blood components that have been donated as such by patients with sporadic CJD and there have been no cases. In terms of plasma the number is probably like 100 to 1, but plasma I wouldn’t expect it. But because there are so many more cases of sporadic CJD. We had several patients years ago and I think the incubation was [inaudible] or something like that, and I think the likelihood of two such cases occurring over a 20 year period -- because you had to figure that was the limit which you could have made the diagnosis, because before 20 years ago no methods were available to detect it. So if you just go back and talk about that, say, 20 year period, the odds of a coincidental pair of cases, a husband and a wife, turn out to be only about 1 in [inaudible], which is counter intuitive. I would have thought it would be 1 in gadzillions.

MP: And so someone ran the statistics off?

PB: Yeah, the statisticians. If you look in the paper though I think it’s in the appendix. I think we published that in *Neurology*. That was just shocking that it was so low, but 1 in 50 is a good deal different than 1 in 20,000.

MP: Right, that’s true in terms of the transfusion -- exactly. So you say 20 years ago CJD was not very well diagnosed.

PB: 20 years ago in 1982 -- you might go 25 years. The last quarter century has seen enough in diagnosis, most from the aspect of refining clinical criteria and the addition of a couple of laboratory aids, so that today any neurologist who has even a casual association with CJD should be able to make the diagnosis in 1992 --

MP: What laboratory aids where there?

PB: Well, the two new ones, but we have had others a long time, but that also has been refined recently and depending on how many you knew. In South America, up to 90% of, but you and under those circumstance it’s a little better than half. So that was a big help, but now we have a spinal fluid protein, 3 which, in the right clinical setting, that is to say if you’re not talking about hypoxia or hypoxic this or herpes encephalitis -- you know, if it’s a dementia that looks like CJD then the test is better than 90% specific and that’s better. In a paper that I just reviewed, it has now quantified the new diagnostic sensitivity by the MRI. The MRI lights up global and global is defined as [in] basal ganglia in about 60%. So you’ve got like 60% EEG, 60% MRI and 90%. That’s pretty damn good and that’s -- plus the clinical findings and we’ve got a lock almost all the time. Well at the outset if you go back in time, even today you can only have an idea. When someone comes and tells me, “I feel a little clumsy,” and they’ve been forgetful immediately I think CJD, but there are all kinds of other things that can happen including nothing. But typically you won’t see a doctor, I think, unless you’ve got something with those symptoms. I mean forgetfulness, yes, but forgetfulness coupled with some physical sign -- that’s pretty usual, that means there’s trouble. But it could be Alzheimer’s, it could be any number of -- there are a number of cerebellar degenerations that do not carry names because they’re not -- the cause is not known. There’s -- I can’t even reel them off the top of my head.

MP: Right I understand. So when you first entered the field and you first started to see patients with CJD how were they being identified at the time?

PB: Clinically, actually a lot of them were being tested unfortunately, by brain biopsies because they were unsure of the diagnosis. There are always alternative diagnoses and so that was a widespread practice that typically lead to mortality due to biopsy, 15 -- 20%, so it was not a harmless procedure. You’re going to get a little snip-snip-snip in the middle of it. It was not a harmless procedure, it never is. We would discourage that. You don’t do that. You don’t need it anymore on a patient because you want to make a diagnosis.

MP: Even if you’re unsure of the diagnosis.

PB: Sure. There’s no public health threat for sporadic CJD and who’s it going to make feel better? The doctor?

MP: What do you think about the risk of transmission by neurosurgery?

PB: Practically almost zero. That’s another thing that’s been looked at for a long time pretty carefully and in particular systematically for many years now and in European studies of CJD and surveillance. You don’t make any money on any association neurosurgery and CJD. It’s a little surprising in view of the infinitesimal amount of infected tissue that is required. It was judged by, for example, electrodes in Switzerland of the wasp. They were subjected to hide vapor and treated up and so forth and there was a bit of infectivity up there on the inside of the electrode, because the outside was effectively wiped clean. I mean an almost invisible amount, in fact I think to the naked eye. An invisible amount infectious of brain tissue. So it’s a little surprising in view of the fact that we can be pretty sure that over the past 20 odd years there have been any number of operations conducted with instruments that have been subjected to routine cleaning and we simply do not find reports or even non-reports of CJD.

MP: Well, there was the woman at the CJD advisory committee meeting?

PB: Yeah, yeah.

MP: Her husband who got CJD.

PB: But she didn't know. He'd certainly gotten neurosurgery, but that whole discussion was obscured in terms of what we're talking about here; the accidental transmission by a total absence of knowledge that any of the operations did in fact have and were conducted in hospitals where there might have been a CJD patient operated on roughly in the same period of time. That's the kind of shoe leather epidemiology that has to be done. We did the same thing in France on two patients.

MP: You looked?

PB: We looked very hard. We went to the -- you know we grilled people in these hospitals and there were two instances in which there had been a possibility and neither one worked out. A third did. It's one of the only probable cases of neurosurgery transmission.

MP: Where was this one from in France?

PB: In Paris.

MP: In Paris, and this was one that you looked at along with?

PB: No I don't think I located it. I think that when we first started looking at it, there was another neurologist and neuropathologist in another hospital who brought that to our attention and I always thought that this was probably a secondary transmission and the circumstances were inconclusive. It had been in three days, it was the same operating suite and you would be hard pressed again not to make a connection between these patients. But in other places there was one patient in a totally independent separate unit and the instruments were never exchanged and we just tracked every possible one and that's been true of other incidences as well. Even the British historical transmissions -- and I think there are only two cases. Bob Will actually ran those down and looked very carefully at them and it looked as though probably two of those were neurosurgery cases were transmitter cases, but those two and the one in France, which is presumptive -- they're all presumptive, none of them are proven. The only proven instance of neurosurgery transmission is the original case from Switzerland where he took the electrode -- one of the two electrodes, implanted it in a chimpanzee and the chimpanzee died of CJD.

MP: Were you involved with that experiment?

PB: Not closely, no. I think that was probably done around the case where -- was that the second or third case? The first case I guess was the corneal implant that was Cornell. I think that was the case. Next came three or four years later, like '77, which means that this experiment would have been done presumably very soon after the neurosurgeon actually came to work in our laboratory.

MP: You mean the Swiss neurosurgeon worked in your laboratory?

PB: Yeah, and actually left medicine to work -- because he was so profoundly affected by what happened, but we'll remember his name pretty soon so he probably came over with the electrodes, if I'm not mistaken. Anyway, my guess is that the transmissions probably occurred. Exactly why, I didn't get involved in that, I don't know. I really don't know. I remember the incident pretty well.

MP: Did he do the experiment himself?

PB: I don't know.

MP: Yeah, okay.

PB: Whatever the paper that described that as I recall came out late.

MP: There was.

PB: Probably published, Joe Gibbs was the senior author on that and that may well be the reason I left it alone. Joe was an interesting guy and one of the things that he did frequently was jealously guard little parts of research for himself. He wouldn't tell other people about it and wouldn't let other people participate. Apparently, he didn't want other people to steal the show from him. I'm not sure he tried to do something with the same thing on the one hand but on the other hand he rather generously put me up as the chairman of the committee to study it. So you know, sort of one hand takes away and the other hand gives so he's a complicated guy. So that may well be the reason. I think we already had the Fredrick facility. Fredrick is where we kept a lot of primates.

MP: Fredrick, Maryland?

PB: Yeah. We experimented either there or in Louisiana and I don't know where but…

MP: You spent time at those facilities?

PB: Oh yeah I went up -- well yeah, but I only -- they were like one day visits. We used to do experiments. I used to go out and inoculate the rodents. So occasionally primates and experiment with them.

MP: What happened to those facilities?

PB: They were taken away.

MP: I'm very interested in sort of how you've experienced changes in the acceptability of primate research. Were these facilities closed down because it was no longer acceptable to do this or what happened -- how much has that impacted your ability to do these experiments?

PB: Historically, over a period of time I assumed that the animal rights people did sensitize, big time, the NIH with respect to all forms of animal experimentation, but particularly primate and even more particularly chimpanzees. Just exactly how fast that progressed and how the proportion of the contribution, but I can tell you that to do any experiment even if now requires ethical considerations and committee approvals that were just not on the books. Now some of it is a good thing, mistreatment or with treatment, which is much more appropriate if it eliminates the unnecessary use but I don't think the NIH would ever willfully mistreat them. Some places I know have, but not the NIH. So I don't think mistreatment is really an issue. I think the issue was do you really have to do these experiments in animals? Is there any other way you can get this information? In our field the answer is no. It never has been. It is diminished today because of the PRP and experiments that can be done today using PRP as a guide for what, in time, is still going to have to be the final experiment. But in the past we didn't have to look at. In fact no everything had to be done in a bioassay. So the bioassays in our field are no less frequently, but they're almost always needed eventually and that's true and will continue to be true until such time if ever that protein or something else have a 1 to 1 relationship. So it's been increasingly difficult to do animal experiments. They're done but you -- I said that even if I had the money I would think more than twice about ever again trying to do animal experiments again. It is such a hassle. I mean, I sort of joke about pretty soon they're going to have playtime period for the mice everyday. They're going to take them out and walk them. It's really beyond -- it's gotten out of control. In fact, as far as I'm concerned the entire posture of the NIH with respect to "cover your backside so that nobody can criticize you for anything" has gotten out of control. The administration it seems to me should be far more concerned about avoiding criticism. I'm glad to be closing out of a career instead of beginning.

MP: Yeah, I understand.

PB: There's a balance. I understand why you don't want to be criticized but it seems to me that if some of these administrators had a little more backbone and stood up to the people who are promoting these policies that are out of control that they would be far more honest and to do so.

MP: But they're not going to do that?

PB: No, absolutely not. They cave in.

MP: And what about the facilities where you had the primates, did they all shut down?

PB: Well, we don't have them anymore. If the laboratory still existed we would still have primates, but those primates that would be alive, with the exception of the chimps which have a lifetime on staying on alive, but monkeys for example are no longer useful for purposes of observation and bioassays, but were inoculated a long time ago. Let's say they were inoculated with HIV or they were inoculated with Alzheimer's or with some other disease that we just hadn't to transmit it in to 60 years, then they're euthanized. So little by little, I think our leftover animals -- the numbers are shrinking with the exception of the chimp. They're a burden to everybody and they should be euthanized.

MP: You can't [inaudible] them --

PB: You can't do anything to them. You can't give them to zoos, because they've been inoculated even if it's something not dangerous, they won't know for sure.

MP: But there are laws.

PB: Yeah. Well I don't know about the laws on that.

MP: But ethically --

PB: Yeah and there are certainly -- it has been now generally conceded that you have to. In our field we don't need to with one exception. Obviousl. I just read one of the cases that we used as it turned out for studying blood infectivity, one of those cases -- in fact the case that there was a transmit from blood, was a patient with a mutation and this patient had had an appendectomy a month before the onset of symptoms. As we looked at all the patients' friends, there were lots of stories about events that happened within the past weeks and days before the onset of symptoms, or they got something like the flu and never really recovered. These were all anecdotes and we wondered whether if you took 200 people and asked them if anything so traumatic had happened to them in the previous few six months you'd probably get a fair amount of them that would say, "Yes." So you can't really trust that kind of looking back.But you could study it. You could do a study if hasn't been done one, someone ought to do that. Someone could take 400 or 500 people or 1,000 people. A nice number and ask them if anything unusual or traumatic or upsetting or seriously upsetting or anything physical of a serious nature had happened to them during the previous six months and you do the same thing -- where we know already the answer in Europe is quite a lot of them. We know the answer in France from the studies we did many years ago. Now that the European case control studies with about 500 patients who were used as non CJD controls, that was not one of the questions that was asked. Otherwise we'd have the answer now.

MP: Yeah, that's too bad,when I was looking at CJD I don't know how many.

PB: They have all these stories.

MP: Exactly.

PB: That's why I joked that it just opened up a flood gate of litigation.

MP: Oh gosh.

PB: I actually was recounting a true story.

MP: That dog one?

PB: Yeah, when I said that the guy went out --in fact I think it was '86. The father left the house one day and the dog next door surprised him and he fell down and hurt himself and then like two weeks later or one week later or -- anyway, fairly close, a small interval of time passed and he started to getting the symptoms. Well, even without this experiment on the books it's not and unfortunately never will be, because of the fact that it was done in chimps and it would need chimps to control it. They were already thinking of cause and effect. When you're dealing with an infectious disease you're always thinking cause and effect. You always want to know why did it happen 1) to me, 2) when it did and that will continue until we find out.

MP: What we're talking about in hamsters, but he ran into the problem that he couldn't find pharmacological and physiological stress in hamsters, but you said you gave up on the experiment because you couldn't find one because the excuse that could be used for everything. Like if you gave them amphetamines, high doses of amphetamines, and they didn't even flinch apparently.

PB: Well, judging from the chimps maybe -- actually it's not just that the chimps were not only under general -- they were under general anesthesia for 2 -- 3 hours, but they were also being with blood pressure ups and downs, there are oxygen ups and downs and it's not just a question of sort of going to sleep. There's blood volume ups and downs and even though it's an aphaeresis it's traumatic obviously and it's just too much to overlook all six chimps came down with HIV in about eight months post inoculation. The youngest chimp I ever saw get the disease without being sacrificed in an asymptomatic state was 13 months. It's impossible not expose them to and if it had been 1 out of 6 -- but that's 6 out of 6.

MP: That is coming down earlier than you'd ever seen.

PB: I may try to publish that report somewhere even without any controls.

MP: Do you mind if we switch gears now, and I wanted to ask you about the earlier part of your life and how you decided to become a part of this lab? So, what were you doing prior to joining the lab here, where did you go to school and what were you doing?

PB: Well, I went to Hopkins.

MP: Okay.

PB: And the anatomy professor, who was named Dr. David Bodian, was a very serious guy, but he's very, very, very good scientist and probably should have shared the Nobel Prize.

End of transcript